REMARKS

Claims 1, 3-6, and 8-36 were pending at the time of the Office action. Claims 33 and 34 have been withdrawn from consideration. Claims 1, 3, 4, 6, 8-20, and 29 stand rejected under 35 U.S.C. § 102. Claims 1, 3-6, 8-32, 35, and 36 stand rejected under 35 U.S.C. § 103. Applicant addresses these rejections as follows.

Interview with Examiner Mi

Applicant thanks Examiner Mi for the courtesy of an in-person interview on February 17, 2009. During the interview, the anticipation rejection of claims 1, 3, 4, 6, 8-20, and 29 and the obviousness rejections of claims 1, 3-6, 8-32, 35, and 36 were discussed. As was discussed during the interview, Applicant submits that claims 1, 3-6, 8-32, 35, and 36 are in condition for allowance and respectfully requests that the Examiner contact the undersigned by telephone in order to resolve any remaining issues in this case should the Examiner disagree.

Rejections under 35 U.S.C. § 102

Claims 1, 3, 4, 6, 8-20, and 29 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Bickers et al. (*The Journal of Dermatology* 27: 691-695, 2000; herein "Bickers"), as evidenced by Dou et al. (U.S. Patent Application Publication No. 2002/0151582; herein "Dou"). According to the Examiner, Bickers teaches that "green tea, black tea and constituent polyphenols protect against chemical- and ultraviolet B (UVB)-induced carcinogenesis and reduce the growth of established tumors in skin" (Office action, page 3). The Examiner cites Dou as evidentiary support that the green tea extracts of Bickers contain polyphenolic compounds (e.g., EGCG). This rejection is respectfully traversed.

The present claims are directed to a method of treating precancerous lesions (e.g., actinic keratoses) by administration of a polyphenol-containing composition to a patient. Applicant has demonstrated the effectiveness of this method and describes these results in

Examples 1 and 2 of the specification as filed. As described, patients with established precancerous lesions were treated in a clinical setting with a polyphenol-containing composition, and this treatment resulted in the complete elimination of the lesions.

As discussed with the Examiner, Bickers does not anticipate the present claims because this reference fails to teach a method for treating a precancerous lesion of the skin by administering a pharmaceutically effective amount of a polyphenol to a patient, as required by claim 1. In contrast to the claimed methods, Bickers instead teaches the prevention of a precancerous lesion, a result far different from the treatment of an already established precancerous condition.

Turning specifically to the passages of Bickers cited by the Examiner, Applicant notes that each of these passages refers to either the protective effect of standardized green or black tea extracts or the treatment of cancerous lesions, as Applicant's representative discussed with the Examiner during the in-person interview. In particular, the Examiner cites the following passage from Bickers (page 693 of Bickers, right column):

> [O]ral administration of green tea extract prior to or during multiple PUVA treatments of SKH-1 hairless mice reduces hyperplasia, hyperkeratosis, erythema and edema.

In this experiment described in Bickers, green tea extract was administered to mice (lacking precancerous lesions) prior to or during psoralen-UVA (PUVA) treatment, resulting in the protection against adverse downstream effects of PUVA administration. This experimental result is consistent with Bickers' own characterization that "green tea was... shown to afford protection against PUVA-induced early damage in skin" (page 693 of Bickers, left column), demonstrating Bickers' teaching of preventing (rather than treating) precancerous lesions.

The Examiner also cites experimental studies which demonstrate that "[b]oth black and green tea and their constituents inhibit the tumor initiation, promotion and malignant progression stages of multi-step skin carcinogenesis" (page 693 of Bickers, left column).

This passage of Bickers references the experimental results generated by Mukhtar et al. (*Toxicological Sciences* 52: 111-117, 1999; herein "Mukhtar"). Mukhtar, however, fails to teach the treatment of precancerous lesions and instead describes the administration of green tea or its constituents to cancerous cells, as Applicant's representative discussed with the Examiner. Specifically, Mukhtar (citing Ahmad et al., *Journal of the National Cancer Institute* 89: 1881-1886, 1997; herein "Ahmad") states that treatment with epigallocatechin-3-gallate (EGCG) stimulates apoptosis of cultured cancer cells (e.g., HaCaT, L5178Y, and DU145 cells), but does not stimulate apoptosis of normal human epidermal keratinocytes (see, e.g., the abstract of Ahmad). Thus, the experimental results obtained by Mukhtar and Ahmad (relied upon by Bickers) relate only to the treatment of cancerous cells, and teach nothing about the effects of the administration of a polyphenol on precancerous cells (as required by claim 1). Furthermore, the results from administration of a green tea constituent to the cultured cancerous cell lines of Mukhtar are of questionable relevance to the clinical applications of polyphenols to cells in patients, again as required by the present claims. Indeed, Ahmad states that such results "need to be evaluated in human trials" (Abstract of Ahmad). Therefore, Bickers, alone or as evidenced by Dou, fails to teach all of the elements of claims 1, 3, 4, 6, 8-20, and 29, and Applicant respectfully requests that this rejection of the claims under 35 U.S.C. § 102 be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1, 3-6, 8-26, and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bickers, as evidenced by Dou. This rejection is respectfully traversed. Bickers, as evidenced by Dou, fails to support a *prima facie* case of obviousness. As described above and discussed with the Examiner, the Bickers teaching relates only to the prevention of a precancerous lesion or the effect of green tea extract on cancerous cells. These references provide no teaching to suggest that established precancerous lesions could, or should, be treated with a polyphenol-containing composition. Accordingly,

Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 103(a) be withdrawn.

Claims 1, 3-6, 8-32, and 35 stand further rejected under 35 U.S.C. § 103(a) as being unpatentable over Bickers in view of Brash et al. (U.S. Patent Application Publication No. 2002/0198161; herein "Brash") and further in view of Voet (U.S. Patent No. 6,723,750; herein "Voet") as evidenced by Dou. Brash and Voet fail to cure the deficiencies of Bickers, as neither indicates that polyphenol-containing compounds treat precancerous lesions. Reconsideration and withdrawal of this second basis for the rejection is also respectfully requested.

Claim 36 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Bickers in view of An et al. (*Photochemistry and Photobiology* 76: 73-80, 2002; herein "An"). The Examiner states (Office action, page 15):

> It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the green tea extract to treat actinic keratoses from [An] since [An] teach[es] green tea extract (1 mg/cm^2) largely abrogated the acute COX-2 response to UVB in mice or humans.

Applicant submits that An fails to cure the deficiencies of Bickers, as An does not teach or suggest the treatment of precancerous lesions, such as actinic keratoses. An teaches the topical administration of green tea polyphenol (GTP) extract to murine or human skin prior to UVB irradiation, resulting in the subsequent attenuation of COX-2 expression in the treated cells. An fails to teach or suggest that GTP extract treats an established lesion (e.g., actinic keratoses). Indeed, An states (pages 78-79):

> [T]he observed decrease in COX-2 expression in both murine and human skin receiving a topical application of GTP suggests that GTP may act as a chemopreventive agent by blocking this target.

Accordingly, Applicant respectfully requests that this rejection of claim 36 under 35 U.S.C. § 103(a) be withdrawn.

Zhao et al.

For the record, Applicant also addresses the Zhao et al. reference (*Photochemistry and Photobiology* 70: 637-644, 1999; herein "Zhao"), submitted herewith, a reference that was discussed briefly during the in-person interview of February 17, 2009. Applicant submits that Zhao does not teach or suggest the presently claimed invention because this reference fails to disclose a method for treating a precancerous lesion of the skin by administering a pharmaceutically effective amount of a polyphenol to a patient, as required by claim 1.

In contrast to the claimed methods, Zhao teaches the oral and topical administration of standardized black tea extract (SBTE) for the purpose of preventing UVB-induced inflammation and erythema in murine and human skin prior to and immediately following UVB exposure. For example, Zhao describes the oral administration of SBTE to SKH-1 mice (lacking precancerous lesions) two weeks prior to UVB irradiation. Similarly, individual tea fractions were topically administered to murine and human skin (again, lacking precancerous lesions) minutes before the application of a single dose of UVB irradiation (see, e.g., page 639 of Zhao, sections entitled "Studies in mice" and "Studies in human subjects"), and the irradiated sites were treated with a topical application of SBTE five minutes following UVB exposure. In both mice and humans, administration of SBTE prior to and immediately following UVB exposure protected against UVB-induced erythema (see, e.g., Table 1 and Figure 4).

The protective effect of SBTE demonstrated by Zhao is exemplified in the data presented in Table 1, which shows that the application of SBTE prior to UVB irradiation is more effective in reducing the severity of erythema than the application of SBTE after exposure (severity index of 1.9 ± 0.2 with treatment prior to UVB exposure compared to a severity index of 2.4 ± 0.3 after exposure). Based on Zhao's experimental results, one of skill in the art would conclude that the extract should be administered prior to UVB irradiation to reduce redness and swelling of the skin. Such results would not, however, lead one of skill in the art to conclude that the administration of a tea extract could be

used in the treatment of a precancerous lesion, a condition that could emerge years after UVB-induced skin damage. These experimental results are consistent with Zhao's own conclusion that "black tea extracts and their fractions protect against UVB-induced phototoxicity" (page 642 of Zhao, right column), demonstrating Zhao's teaching of preventing (rather than treating) skin damage. Accordingly, Applicant respectfully submits that Zhao fails to teach or suggest the present claims.

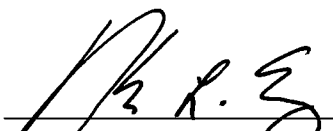
CONCLUSION

Applicant submits that the claims are now in condition for allowance, and such action is respectfully requested. Applicant notes that the Form PTO 1449 that was submitted with an Information Disclosure Statement (IDS) filed on November 26, 2008 has not been initialed and returned, and hereby requests that it be initialed and returned with the next Office action. Applicant also notes that the Examiner has not initialed the Linden et al. citation on the Form PTO 1449 that was submitted with the IDS filed on August 31, 2006 and requests that this Form PTO 1449 be initialed and returned.

Transmitted herewith is a Petition to extend the period for replying to the Office action for two months, to and including May 8, 2009, and payment of the required extension fee. If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 04 May 2009



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